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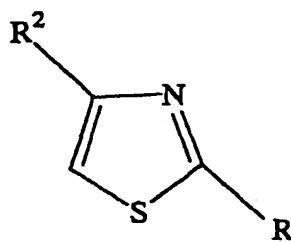
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(54) Title: USE OF THIAZOLE DERIVATIVES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT
OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

(1)

(57) Abstract: The present invention provides a useful and highly safe agent for curing chronic obstructive pulmonary disease, which contains, as the effective ingredient, at least one compound selected from the group consisting of thiazole derivatives and salts thereof represented by the general formula (1), wherein, R¹ is a phenyl group which may have 1 to 3 lower alkoxy groups as the substituents on the phenyl ring; R² is a pyridyl group which may have 1 to 3 carboxyl groups as the substituents on the pyridine ring.

DESCRIPTION

AGENT FOR CURING CHRONIC OBSTRUCTIVE
PULMONARY DISEASE

TECHNICAL FIELD

The present invention relates to an agent for the treatment of chronic obstructive pulmonary disease.

5 BACKGROUND ART

Chronic obstructive pulmonary disease (COPD) is characterized by the progressive development of airflow limitation (airway obstruction) (Pauwell R. A., et al.: Am. J. Respir. Crit. Care Med., 2001 (163), 10 1256-1276).

COPD is one of the major causes of chronic morbidity and mortality throughout the world, and in the Asia-Pacific region, it is also foreseen that patients of COPD will rapidly increase within about 20 15 years from now on, due to the growth of smokers and the aging population.

A diagnosis of COPD should be considered in smokers who have clinical symptoms and signs, such as progressive developing abnormal shortness of breath, 20 associated with airflow obstruction. For this reason, every country in the world has been paying much attention to diagnosis and treatments of COPD.

At present, as to drug therapy for the treatment of COPD, certain drugs such as β_2 -stimulants,

anticholinergic agents and the like, having bronchodilatory action are tentatively used for preventing or suppressing the symptoms. However, these drugs having bronchodilatory action cannot exhibit an 5 improvement in deterioration of the pulmonary function for long period of time, which is the characteristic of COPD and the most important clinical index.

Regarding the effect of steroids, having potent inhibitory effect on the production of 10 cytokines, as an inhalant have been assessed in plural clinical studies in large scale. However, most of them also showed that steroids could not improve the deterioration of the pulmonary function for long period of time (Pauwels R. A., Lodahl C. G., Laitinen L. A., 15 Schouten J. P., Postma D. S., Pride N. B., et al: N. Engl. J. Med., 1999 (340), 1948-1953; Vestbo J., Sorensen T., Lange P., Brix A., Torre P., Viskum K.: Lancet, 1999 (353), 1819-1823; Burge P. S., Calverley P. M., Jones P. W., Spencer S., Anderson J. A., Maslen 20 T. K.: BMJ, 2000 (320), 1297-1303)).

Regarding the drugs having inhibitory effect on the production of active oxygen, any reliable clinical studies have not been examined as yet.

N-acetylcysteine is an antioxidant having a 25 similar effect to that of agents having inhibitory action on the production of active oxygen. While, clinical study showed that N-acetylcysteine could reduce the acute exacerbation rate of COPD (C. Stey, J.

Steure, S. Bachmann, T. C. Medici, M. R. Tramer; Eur. Respir. J., 2000, (16), 253-262). However, there are no reports at all, that N-acetylcysteine shows to improve the deterioration of the pulmonary function in 5 COPD patients for long period of time.

Furthermore, clinical studies are conducting to examine whether the drugs inhibiting phosphodiesterase IV activity will be the treatment of COPD. However, it has been reported that these drugs 10 have adverse side-effects as well, for example, nausea, vomiting and increasing the secretion of acid in the stomach (Peter J. Barnes: N. Engl. J. Med., 2000 (343) No. 4, 269-280).

As is explained above, there are no drugs 15 having improvement in deterioration of the pulmonary function in COPD, as well as having sufficient ability as a drug for the treatment of COPD, which have yet been developed.

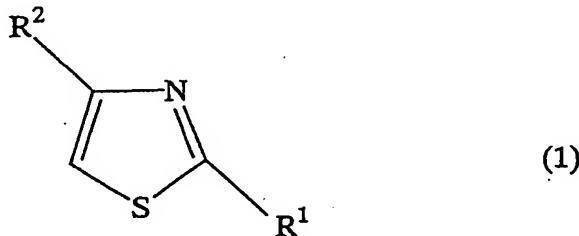
DISCLOSURE OF THE INVENTION

20 An object of the present invention is to provide a useful and highly safe drug for the treatment of COPD.

The present inventors have prepared an animal model having the pathogenic features, which is 25 clinically very close to COPD, and have conducted extensive research works by use of this animal model. As the result, the inventors have found the facts that

some of thiazole derivatives, which are disclosed in JP-A-5-51318, JP-A-10-152437, EP 513387 A1 and WO98/14191, known as inhibitors for producing active oxygen, producing cytokines and cell adhesion, possess 5 improving effects on the deterioration of the pulmonary function, such as airflow obstruction, thus such thiazole derivatives exhibit extremely high effect for curing COPD with lesser side effects like nausea, vomiting and secretion of acid in the stomach with high 10 safety. Finally, the present invention has been completed on the basis of these findings.

1) The present invention relates to an agent for the treatment of COPD characterized by containing, as the effective ingredient, at least one compound 15 selected from the group consisting of thiazole derivatives and salts thereof represented by the general formula (1),



wherein R¹ is a phenyl group which may have 1 to 3 lower alkoxy groups on the phenyl ring; and R² is a pyridyl 20 group which may have 1 to 3 carboxyl groups on the pyridine ring.

(2) The present invention relates to the agent for the treatment of COPD as mentioned in the above 1), wherein the thiazole derivative is 6-[2-(3,4-diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid.

5 BEST MODE FOR CARRYING OUT THE INVENTION

The thiazole derivatives represented by the general formula (1) of the present invention are known compounds, and can be prepared by the methods for example, the method disclosed in JP-A-5-51318.

10 Each one of the groups in the above-mentioned general formula (1) is specifically mentioned as follows.

As for a phenyl group which may have 1 to 3 lower alkoxy groups as the substituents on the phenyl 15 ring, there can be exemplified a phenyl group which may have 1 to 3 straight- or branched-chain alkoxy groups having 1 to 6 carbon atoms, as the substituents on the phenyl ring, such as phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-pentyloxyphenyl, 3-ethoxy-4-methoxyphenyl, 4-hexyloxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 2,3-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3-propoxy-4-methoxyphenyl, 3,5-dimethoxyphenyl, 3,4-dipentyloxyphenyl, 3,4,5-trimethoxyphenyl, 3-methoxy-4-ethoxyphenyl groups and the like.

As for a pyridyl group which may have 1 to 3 carboxyl groups as the substituents on the pyridine ring, there can be exemplified a pyridyl group which may have 1 to 3 carboxyl groups as the substituents on the pyridine ring, such as pyridyl, 2-carboxypyridyl, 3-carboxypyridyl, 4-carboxypyridyl, 2,3-dicarboxypyridyl, 3,4-dicarboxypyridyl, 2,4-dicarboxypyridyl, 3,5-dicarboxypyridyl, 3,6-dicarboxypyridyl, 2,6-dicarboxypyridyl, 2,4,6-tricarboxypyridyl and the like.

Among the thiazole derivatives represented by the general formula (1) of the present invention, a compound having basic groups can form a salt thereof with pharmacologically acceptable acids. As to such acids, there can be exemplified inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid and the like; and organic acids such as acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, succinic acid, benzoic acid and the like.

Among the thiazole derivatives represented by the general formula (1) of the present invention, a compound having acidic groups can form a salt thereof with pharmacologically acceptable basic compounds. As to such basic compounds, there can be exemplified sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogen

carbonate and the like.

The thiazole derivatives of the present invention include their optical isomers.

Generally, a compound represented by the 5 general formula (1) is used in the forms of common pharmaceutical preparations.

The pharmaceutical preparations are prepared with conventional diluents or excipients such as fillers, diluents, binders, wetting agents, 10 disintegrators, surface active agents, lubricants and the like.

As to the pharmaceutical preparations desired unit forms can be selected depending on the curing purposes. Typical unit forms include tablets, pills, 15 powders, liquids, suspensions, emulsions, granules, capsules, suppositories, injections (liquids, suspensions, etc.), inhalants and the like can be exemplified.

For shaping in tablet form preparation, any 20 carriers widely used in this field can be used.

Examples of carriers include excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid; binder such as water, 25 ethanol, propanol, simple syrup, glucose, starch solution, gelatin solution, carboxymethyl cellulose, shelac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone; disintegrators such as dried

starch, sodium alginate, agar-agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium laurylsulfate, monoglyceride of stearic acid, starch and lactose; disintegration inhibitors such as white sugar, stearin, cacao butter and hydrogenated oil; absorption accelerators such as quaternary ammonium base and sodium laurylsulfate; wetting agents such as glycerin and starch; adsorbing agents such as starch, lactose, kaoline, bentonite and colloidal silicic acid; lubricants such as refined talc, stearic acid salts, boric acid powder and polyethylene glycol. If necessary, tablets can be further coated with usual coating materials to make them as sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coatings, tablets coated with films, double layered tablets and multiple layered tablets.

For the purpose of shaping the pharmaceutical composition in the form of pills, any excipients which are known and widely used in this field can be used, for example, carriers such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin, talc and the like; binders such as arabic gum powder, powdered tragacanth, gelatin, ethanol and the like; disintegrating agents such as laminaria, agar-agar and the like.

For the purpose of shaping the pharmaceutical composition in the form of suppositories, any

excipients which are known and widely used in this field can be used, for example, polyethylene glycols, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glycerides and the 5 like.

For the purpose of shaping the pharmaceutical composition in the form of capsules, they are prepared in accordance with a conventional method by mixing the effective ingredient with the above-mentioned various 10 carriers, then filling it in hard gelatin capsules or soft gelatin capsules.

For the purpose of shaping the pharmaceutical composition in the form of injection preparations, solutions emulsions and suspensions are sterilized and 15 are preferably made isotonic to the blood. In making the injection preparations, any diluents usually used in this field can be used, for example, water, ethyl alcohol, polyethylene glycol, propylene glycols, ethoxylated isostearyl alcohol, polyoxylated isostearyl 20 alcohol, polyoxyethylene sorbitan fatty acid esters and the like. In these instances, an adequate amount of sodium chloride, glucose or glycerin may be added to the desired injection preparations to make them isotonic to the blood. Further, usual dissolving 25 auxiliaries, buffering agents, analgesic agents may be added. Yet further, if necessary, coloring agents, preservatives, perfumes, seasoning agents, sweetening agents and other medicines may be added to the desired

pharmaceutical preparations.

Inhalant compositions are prepared in accordance with usual methods. That is, the effective ingredients are made in powder or liquid form, and

5 formulated with an inhalation propellant and/or carrier, then filled in a suitable inhalation container. Further, mechanical powder inhalators conventionally used may be applied in the case that the effective ingredients are in powder form, and

10 inhalators like a nebulizer may be used in the case that the effective ingredients are in liquid form. As to the inhalation propellant, any one known in this field can be used, for example, fluorocarbon type compounds such as flon-11, flon-12, flon-21, flon-22, flon-113,

15 flon-114, flon-123, flon-142c, flon-134a, flon-227, flon-C318, 1,1,1,2-tetrafluoroethane and the like; hydrocarbons such as propane, isobutane, n-butane and the like; ethers such as diethyl ether and the like; compressed gases, such as nitrogen gas, carbon dioxide

20 gas and the like can be exemplified.

If necessary, the inhalant preparations of the present invention may be formulated with surface active agents, oils, seasonings, cyclodextrin or its derivatives and the like, accordingly. As to the

25 surface active agents, there can be exemplified oleic acid, lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropylmyristate, glyceryl trioleate, glyceryl

monolaurate, glyceryl monooleate, glyceryl
monostearate, glyceryl monoricinoate, cetyl alcohol,
stearyl alcohol, polyethylene glycol 400, cetyl
pyridinium chloride, sorbitan trioleate (trade name:
5 Span 85), sorbitan monooleate (trade name: Span 80),
sorbitan monolaurate (trade name: Span 20),
polyoxyethylene hardened castor oil (trade name:
HCO-60), polyoxyethylene (20) sorbitan monolaurate
(trade name: Tween 20), polyoxyethylene (20) sorbitan
10 monooleate (trade name: Tween 80), lecithin derived
from natural sources (trade name: Epikuron), oleyl
polyoxyethylene (2) ether (trade name: Brij 92),
stearyl polyoxyethylene (2) ether (trade name: Brij
72), lauryl polyoxyethylene (4) ether (trade name: Brij
15 30), oleyl polyoxyethylene (2) ether (trade name:
Genapol 0-020), block copolymer of oxyethylene with
oxypropylene (trade name: Synperonic) and the like. As
to the oils, corn oil, olive oil, cotton seed oil,
castor oil and the like can be exemplified.

20 In case of making the effective ingredient of
the present invention as a liquid form preparation,
said effective ingredient may be dissolved in a liquid
form carrier. As to the liquid form carriers, water,
an aqueous solution of sodium chloride, an organic
25 solvent and the like can be exemplified. Among these
carriers, water is preferable. Further, in case of
dissolving, a surface active agent such as
polyoxyethylene glycol having molecular weight of 200

to 5000, polyoxyethylene (20) sorbitan monooleate and the like; sodium carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidon, polyvinyl alcohol or the like may be added thereto.

5 In case of making the effective ingredient of the present invention as in powder form, the ingredient may be pulverized in accordance with usual methods, for example, the ingredient is pulverized into refined powder, by mixing together with lactose, starch or the
10 like so as to make it in a uniform mixture.

The amount of the effective ingredient to be contained in the therapeutical drug of the present invention is not specifically restricted. It can be selected from a wide range, usually it may be contained
15 about 1 to 70% by weight in the desired pharmaceutical composition.

Administration methods of the therapeutical drug of the present invention is not specifically restricted. The therapeutical drug of the present invention can be administered according to the method
20 of use, an age of the patient, distinction of sex, other conditions, condition of the symptoms and the like. For example, tablets, pills, liquids, suspensions, emulsions, granules, and capsules are orally
25 administered. Injection preparations are intravenously administered singly or mixed with injection transfusions such as glucose solutions, amino acid solutions or the like; and if necessary, the injection

preparations are administered singly intramuscularly, intracutaneously, subcutaneously, or intraperitoneally. Suppositories are administered into the rectum. The inhalants are administered into the cavity of mouth.

5 The dosage of the therapeutical drugs of the present invention is suitably selected according to the method of use, an age of the patient, distinction of sex, other conditions, condition of the symptoms and the like, and usually about 0.2 to 200 mg/kg of the
10 body weight per day of the effective ingredient may be administered.

The agent for the treatment of COPD of the present invention possesses excellent improving effect on the deterioration of the pulmonary function, such as
15 airflow obstruction, and exhibits extremely high curing effect against COPD.

The agent for the treatment of COPD of the present invention is a highly safe drug with less adverse side-effects such as nausea, vomiting,
20 secretion of acid in the stomach.

EXAMPLES

The present invention will be explained in detail by illustrating the following Pharmaceutical Preparation Examples and Pharmacological Test Examples.
25 However, the invention are not restricted to these examples.

In the following examples, "Compound A" means

6-[2-(3,4-diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid.

Pharmaceutical Preparation Example 1

	Compound A	150 g
5	Avicel (trade name, manufactured by Asahi Chemical Industry, Co., Ltd.)	40 g
	Corn starch	30 g
	Magnesium stearate	2 g
	Hydroxypropylmethyl celulose	10 g
10	Polyethylene glycol-6000	3 g
	Castor oil	40 g
	Ethanol	40 g

Compound A, Avicel, corn starch and magnesium stearate were mixed together and pulverized. The 15 resulting mixture was subjected to form tablets by use of tableting machine having a punder of 10 mm in diameter. Then film coated tablets were prepared by coating with a film coating agent consisting of hydroxypropylmethyl cellulose, polyethylene glycol-20 6000, castor oil and ethanol.

Pharmaceutical Preparation Example 2

	Compound A	150 g
	Citric acid	1.0 g
	Lactose	33.5 g
25	Dicalcium phosphate	70.0 g

15

	Pluronic F-68	30.0 g
	Sodium laurylsulfate	15.0 g
	Polyvinyl pyrrolidone	15.0 g
	Polyethylene glycol (Carbowax 1500)	4.5 g
5	Polyethylene glycol (Carbowax 6000)	45.0 g
	Corn starch	30.0 g
	Dried sodium stearate	3.0 g
	Dried magnesium stearate	3.0 g
	Ethanol	q.s.

10 Compound A, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate were mixed together. The resulting mixture was sieved through No. 60 screen, then subjected to wet-granulation by using an alcohol solution containing 15 polyvinyl pyrrolidone, Carbowax 1500 and 6000. If required, ethanol was added to the mixture to make it a lump in a paste form. Then corn starch was added thereto and mixing operation was continued until uniform particles were obtained. The resulting mixture 20 was sieved through No. 10 screen, then the sieved mixture was placed on a tray and dried in an oven at 100°C for 12 to 14 hours. Thus obtained dried particles were sieved through No. 16 screen, and dried sodium laurylsulfate and dried magnesium stearate were 25 added to it with stirring. The resultant was compressed to form the desired shape by use of a tabletting machine.

The core portion of the resulting tablets were treated with varnish, and talc powder were spread on the surface of the tablets so as to prevent it from moisture absorption. The under coat layer was coated 5 around the core portion. Varnish coating were conducted with sufficient times, so as to make the tablets for oral administration. For the purpose to make the tablets to form complete spherical shape with smooth surface, further coating operations were 10 conducted to give under coat layers and smooth surface coatings. Color coating were conducted until the obtained tablets had the desired surface coloring. After dried, the coated tablets were polished and had uniform luster.

15 Pharmaceutical Preparation Example 3

	Compound A	5.0	g
	Polyethylene glycol		
	(Molecular weight: 4000)	0.3	g
	Sodium chloride	0.9	g
20	Polyoxyethylene sorbitan monooleate	0.4	g
	Sodium metabisulfite	0.1	g
	Methyl paraben	0.18	g
	Propyl paraben	0.02	g
	Distilled water for injection	10.0	ml

25 The above-mentioned parabens, sodium metabisulfite and sodium chloride were dissolved in a

half volume of the above-mentioned distilled water at 80°C with stirring. Thus obtained solution was cooled to 40°C, then compound A, next polyethylene glycol and polyoxyethylene sorbitan monooleate were dissolved in 5 the above-mentioned solution.

The remaining volume of the distilled water for injection was added to the obtained solution so as to adjust to the final volume, and the resulting solution was filtered and sterilized by use of a 10 suitable filter paper, to prepared the desired injection preparation.

Pharmacological Test Example

In accordance with the method of Jun-ichi Fuchikami, et al. (Japanese Journal of Pharmacology, 15 2000, (82), p. 247), the following pharmacological test was conducted.

Hartley strain guinea pigs (5 weeks age, body weight: 300 to 379.5 g) were exposed to smoke of cigarette (trade name: Hi-Light, manufactured by Japan 20 Tobacco Inc.) for 1 hour/day, 5 days a week, during 4 weeks, by using a flow-past type nose-only inhalation chamber, manufactured by Muenster Co. Control group as a normal group was exposed to the atmospheric air instead of cigarette smoke.

25 Compound A was suspended in 0.5% tragacanth gum aqueous solution, and this suspension was orally administered compulsorily to the guinea pigs (compound

A administered group), in the amount of 10 mg/kg once a day, 1 hour before the exposure to cigarette smoke in the day of exposure, and in the morning in the day of non-exposure, respectively.

5 To the guinea pigs in the vehicle administered group, a 0.5% tragacanth gum aqueous solution without containing Compound A was orally administered instead of the suspension of compound A.

While, to the guinea pigs in the control 10 group, neither the 0.5% tragacanth aqueous solution nor the compound A suspension were administered.

Before exposure and during the period of 4 weeks of exposure to the smoke of cigarette, the respiratory functions (specific airway resistance and 15 peak expiration flow) of the guinea pigs were non-invasively assessed once a week under conscious condition, using Double-chamber Plethysmograph method with a respiratory function measuring equipment (Pulmos-I, manufactured by M.I.P.S. Co.).

20 The respiratory functions (i.e., values of specific airway resistance and peak expiration flow) were obtained as an average of 100 times measured values of the functions, and were shown as the changes of percentage to the respective value of respiratory 25 function measured before exposure to cigarette smoke.

The results are shown in Table 1 and Table 2 as follows.

Table 1. Changes in Specific airway resistance value

Test groups	1 Week after exposure (%)	2 Week after exposure (%)	3 Week after exposure (%)	4 Week after exposure (%)
Control group	-3.23 ± 16.20	-10.60 ± 17.94	-4.35 ± 17.82	7.61 ± 21.57
Vehicle administered group	202.35 ± 65.10 *	188.64 ± 58.07 *	231.34 ± 67.33 **	216.57 ± 55.91 **
Compound A administered group	12.75 ± 7.45 #	41.82 ± 26.91 #	61.08 ± 29.27 #	51.26 ± 24.28 #

(*: P< 0.05, **: P< 0.01: Significant difference from Control group (Student's-test)

#: P< 0.05: Significant difference from Vehicle administered group (Student's-test)

Table 2. Changes in Peak expiration flow

Test groups	1 Week after exposure (%)	2 Week after exposure (%)	3 Week after exposure (%)	4 Week after exposure (%)
Control group	10.31 ± 5.63	8.26 ± 10.15	17.33 ± 12.99	53.57 ± 21.32
Vehicle administered group	-22.57 ± 4.83 **	-10.44 ± 6.90	-2.09 ± 4.48	26.26 ± 5.54
Compound A administered group	9.67 ± 8.48 ##	15.67 ± 14.98 #	14.08 ± 8.48	37.06 ± 11.33

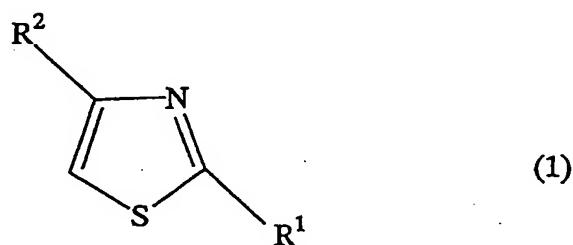
**: P< 0.01: Significant difference from Control group (Student's-test)

##: P< 0.01: Significant difference from Vehicle
administered group. (Student's-test)

As is clearly indicated in the above-mentioned Tables 1 and 2, compound A exhibited 5 excellent improving effects in both parameters of the specific airway resistance and peak expiration flow, as compared with those obtained in the vehicle administered group. Thus, it is clearly shown that the compound A possesses the improving effect on 10 deteriorating the pulmonary function.

CLAIMS

1. Use of a compound for the production of a medicament for the treatment of chronic obstructive pulmonary disease, which medicament comprises, as the effective ingredient, at least one compound selected from the group consisting of thiazole derivatives and salts thereof represented by the general formula (1),



wherein R¹ is a phenyl group which may have 1 to 3 lower alkoxy groups as the substituents on the phenyl ring; R² is a pyridyl group which may have 1 to 3 carboxyl groups as the substituents on the pyridine ring.

2. The use according to Claim 1, wherein the thiazole derivative is 6-[2-(3,4-diethoxyphenyl)-thiazol-4-yl]pyridine-2-carboxylic acid.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/07221

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/427 A61K31/4439 A61P11/00 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 08830 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK G.M.B.H., GERMANY; BAR, THOMAS; ULR) 5 March 1998 (1998-03-05) page 1, last paragraph -page 9, line 18 page 20, line 1 - line 18 claims 1-9 ---- -/-	1,2

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 14191 A (CHIHIRO MASATOSHI ;YAMASHITA HIROSHI (JP); MIYAKODA GORO (JP); MOR) 9 April 1998 (1998-04-09) cited in the application page 6, line 21 -page 8, line 1 page 9, line 12 - line 13 page 10, line 5 page 15, line 21 - line 24 page 18, line 11 page 19, line 7 -page 23, line 12 page 43; example 2 page 51; examples 26,27 claims 1-18 —	1,2
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Information on patent family members

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